REMARKS

The Examiner rejected claims 1-33. Applicants acknowledge the Examiner's finding that original claims 9 and 15 are free of the prior art. Claims 1-8, 10-14, and 16-33 have been cancelled herein without prejudice. In addition, claims 9 and 15 have been amended, and claims 34-66 have been added. Thus, claims 9, 15, and 34-66 are pending.

Original claims 9 and 15 depended from claim 1. Claim 1 has been cancelled, and claims 9 and 15 have been rewritten in independent form incorporating language of original claim 1. In addition, claim 15 has been amended to indicate that the nucleic acid produces the recited mRNA levels in cells *in vitro*, regardless of the mRNA levels obtained *in vivo*. New claims 34-48 depend from amended claim 9 and are similar to the original claims. New claims 49-66 depend from amended claim 15 and are similar to the original claims. Support for these amendments and new claims can be found throughout Applicants' specification and original claims. Thus, no new matter has been added.

In light of the following remarks, Applicants respectfully request reconsideration and allowance of claims 9, 15, and 34-66.

Information Disclosure Statement

Applicants respectfully note that an initialed copy of the PTO-1449 form mailed October 18, 2001 has not been returned. Thus, Applicants respectfully request return of an initialed copy. For the Examiner's convenience, a copy of the PTO-1449 form mailed October 18, 2001 is attached hereto. In addition, copies of the listed references can be resubmitted upon request.

Objections to the Specification

The Examiner objected to the description of the drawings for Figure 3A and Figure 4. Applicants have amended the description for Figure 3A to recite "Thr115" in place of "Thr11" as suggested by the Examiner. In addition, Applicants have deleted the duplicate description for Figure 4. No new matter has been added by these amendments.

The Examiner also objected to the description of Figure 9 stating that it is not consistent with Example 7. Applicants have amended Example 7 to reference Figure 10 as opposed to

Figure 9. A person having ordinary skill in the art would have appreciated that the results discussed in Example 7 relate to Figure 10, not Figure 9. Thus, no new matter has been added.

In addition, the Examiner objected to the label of Figure 10B because it is not clear which construct is used for lanes 4 and 5. The HSE-Tyr 300-FULL-GM-CSF construct was used for lanes 4 and 5. A person having ordinary skill in the art would have appreciated that these lanes contained an HSE-Tyr300 construct, especially given the disclosure in Example 7.

The Examiner objected to the description of Figure 13 asserting that the description of Figure 13 "cannot correctly reflect the data." A person having ordinary skill in the art reading Applicants' specification would have understood the data presented in Figure 13. For example, each well presented in Figure 13 is identified by both the cell type and treatment used. Applicants note that the description of Figure 13 has been amended herein to correct a minor typographical error. No new matter has been added by this amendment.

The Examiner objected to the embedded hyperlink at page 14, line 18 of the specification. Applicants have amended page 14, line 18 to remove the embedded hyperlink. No new matter has been added.

In light of the above, Applicants respectfully request withdrawal of the objections to the specification.

Rejections under 35 U.S.C. § 112, second paragraph

The Examiner rejected claims 14 and 24 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 14 and 24 have been cancelled herein without prejudice. Thus, this rejection is moot.

Rejections under 35 U.S.C. § 112, first paragraph

The Examiner rejected claims 1-24 and 27-33 under 35 U.S.C. § 112, first paragraph, because "the specification, while being enabling for Tyr300 promoter operably linked to a cytotoxic gene for killing melanoma cells by local infection, does not reasonably provide enablement for treating a patient in need of tissue-selective gene therapy for any diseases using

the same vector or a two component vector system with HSE/HSF-1 regulation *in vivo*." The Examiner also stated that:

> The specification does not provide evidence or guidance for regulation of any transgene expression in vivo. There is also no evidence that any construct especially construct encoding a cytotoxic gene can have the transgene expression to reach 100-fold higher in the gene expression level under any promoter in any target cell than non-targeted cells in vivo (pertaining to instant claims 15-17).

In addition, the Examiner stated that:

> As the specification fails to provide any evidence or teaching to teach the skilled artisan how to use any vector such a vector comprising Tyr300 promoter to encode any transgene to any specific tissue of any animal so that the transgene expression can be regulated under the control of HSF-1 in vivo for treating any tumor or disease, the claimed methods are not enabled.

Applicants respectfully disagree. A person having ordinary skill in the art at the time Applicants filed would have been able to make and use the originally claimed invention without undue experimentation. To further prosecution, however, claims 1-8, 10-14, and 16-33 have been cancelled herein.

Independent claims 9 and 15 recite compositions. In addition, claim 15 has been amended to indicate that the nucleic acid produces the recited mRNA levels in cells *in vitro*. A person having ordinary skill in the art at the time Applicants filed would have been able to make and use the presently claimed compositions without undue experimentation. In fact, a person having ordinary skill in the art at the time Applicants filed, using common molecular cloning techniques, would have been able to follow the extensive teachings provided throughout Applicants' specification to make a composition containing nucleic acid having a cell type-specific promoter, a therapeutic gene sequence, an amplification promoter element, and a sequence encoding a transcription activator. Moreover, a person having ordinary skill in the art at the time Applicants filed would have been able to assess mRNA levels produced by cells *in vitro* using, for example, standard RT-PCR assays as described in Example 7 of Applicants' specification. Thus, claims 9 and 15 are fully enabled.

Rejections under 35 U.S.C. § 102(b)

The Examiner rejected claims 1, 2, 4-7, 19, 21, 22, and 27 under 35 U.S.C. § 102(b) as being anticipated by Wu *et al.* (U.S. Patent No. 5,756,343).

Applicants respectfully disagree. To further prosecution, however, claims 1, 2, 4-7, 19, 21, 22, and 27 have been cancelled herein without prejudice. Thus, these rejections are moot.

Rejections under 35 U.S.C. § 102(e)

The Examiner rejected claims 1, 2, 4-7, 11, 13, 21, and 25 under 35 U.S.C. § 102(e) as being anticipated by Baird *et al.* (U.S. Patent No. 6,037,329).

Applicants respectfully disagree. To further prosecution, however, claims 1, 2, 4-7, 11, 13, 21, and 25 have been cancelled herein without prejudice. Thus, these rejections are moot.

Rejections under 35 U.S.C. § 103(a)

The Examiner rejected claims 1, 3, 8, and 11-13 under 35 U.S.C. § 103(a) as being unpatentable over Wu *et al.* (U.S. Patent No. 5,756,343) in view of Baird *et al.* (U.S. Patent No. 6,037,329) further in view of Russell *et al.* (U.S. Patent Application US 2002/0042147 A1). The Examiner also rejected claims 1, 3, 8, and 11-13 under 35 U.S.C. § 103(a) as being unpatentable over Wu *et al.* (U.S. Patent No. 5,756,343) in view of Vile *et al.* (*Cancer Res.*, 54:6228-6234, 1994) further in view of Russell *et al.* (U.S. Patent Application US 2002/0042147 A1). In addition, the Examiner rejected claims 1 and 11-13 under 35 U.S.C. § 103(a) as being unpatentable over Wu *et al.* (U.S. Patent No. 5,756,343) in view of Miyanobara *et al.* (U.S. Patent No. 5,739,018) further in view of Russell *et al.* (U.S. Patent Application US 2002/0042147 A1). Further, the Examiner rejected claims 1, 10, 18, and 28 under 35 U.S.C. § 103(a) as being unpatentable over Wu *et al.* (U.S. Patent No. 5,756,343) in view of He *et al.* (*Mol. Cell. Biol.*, 18:6624-33, 1998) further in view of Heta *et al.* (*BBA*, 1397:43-55, 1998). Lastly, the Examiner rejected claims 25 and 26 under 35 U.S.C. § 103(a) as being unpatentable over Coa *et al.* (*In Vivo*, 13:181-187, 1999) in view of Russell *et al.* (U.S. Patent Application US 2002/0042147 A1) further in view of Takeda *et al.* (*Biochem. Biophys. Res. Comm.*, 162:984-990, 1989).

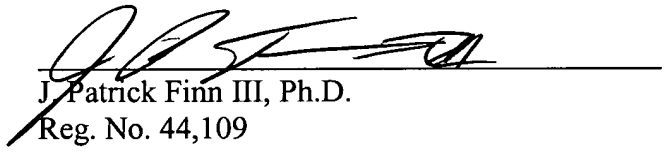
Applicants respectfully disagree. To further prosecution, however, claims 1, 3, 8, 10-13, 18, 25, 26, and 28 have been cancelled herein without prejudice. Thus, these rejections are moot.

CONCLUSION

Applicants submit that claims 9, 15, and 34-66 are in condition for allowance, which action is requested. The Examiner is invited to call the undersigned agent at the telephone number below if such will advance prosecution of this application. The Commissioner is authorized to charge any fees or credit any overpayments to Deposit Account No. 06-1050. Attached is a marked-up version of the changes being made by the current amendment.

Respectfully submitted,

Date: February 27, 2003



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Version with markings to show changes made

In the specification:

The paragraph beginning at page 5, line 9 has been amended as follows:

Figures 3A and 3B illustrate the high selectivity of a human tyrosinase 300 base pair (base pair) promoter element using a nested RT-PCR assay. Figure 3A indicates that the [Tyr 115] Tyr115 base pair promoter is not completely inactive in non-melanoma cells. RT-PCR to determine expression of the CAT gene under the control of the [Tyr11] Tyr115 base pair promoter was performed using RNA from a range of non-melanoma lines (lanes 2 and 3, HT1080; lanes 4 and 5, 293; lanes 12 and 13, A378M). Reverse transcriptase was omitted in the odd numbered lanes. Expression is observed in at least 2 non-melanoma cell lines (293, lane 4 and Tel CeB6, lane 6). Figure [3b] 3B shows the same RT-PCR assay of Figure 3A repeated to determine the expression of a CAT gene under the control of the Tyr300 promoter. Lane assignments are the same as those in Figure 3A.

The paragraph beginning at page 6, line 1 has been deleted:

[Figure 4 demonstrates that HSE confers heat-shock and mHSF-1 inducibility on the melanoma-specific Tyr 300 base pair promoter. MeWo cells transfected with the Tyr 300-GM-CSF (condition 2) or the HSE-Tyr 300-FULL-GM-CSF plasmids (condition 6) express only very low amounts of GM-CSF, demonstrating that Tyr 300 is a very weak promoter. However, transfection of the human melanoma MeWo line with the TDE-5V40-GM-CSF plasmid (condition 3) leads to easily detectable levels of GM-CSF production. In the presence of either heat shock (42 °C, 30 minutes; condition 4) or a co-transfected mHSF-1 plasmid (condition 5), GM-CSF production is increased significantly following transfection with the HSE-Tyr 300-GM-CSF plasmid. Co-transfection of a non-melanoma cell line (HT1080) with the HSE-Tyr 300-GM-CSE plasmid and the HSF-1 cDNA did not yield any detectable GM-CSF production (condition 1).]

The paragraph beginning at page 8, line 1 has been amended as follows:

Figures 13A-F illustrate that the HSE-Tyr-300/HSF-1 feedback loop can be used to kill melanoma cells specifically and efficiently. Figures 13A and 13B show the effects of control (calcium phosphate only) transfections and transfection with CMV-GALV of non-melanoma TelCeB6 cells. Figures 13C-D show the effects of transfections of Me1624 cells with the HSE-Tyr-300 and Tyr-300-GALV constructs[.] gave low levels of toxicity when transfected into a melanoma line, (or MeWo, not shown). Figures 13E-F show the effects of transfection with increasing amounts of co-transfected HSF-1d202-316 β-Gal plasmid.

The paragraph beginning at page 14, line 8 has been amended as follows:

Methods of identifying promoter sequences are routine in the art. For example, in one embodiment of the invention, to identify a promoter sequence, the 5' portion of a gene is analyzed for the presence of sequences characteristic of promoter sequences, such as a TATA box consensus sequence (TATAAT), which is usually an AT-rich stretch of 5-10 base pair located approximately 20 to 40 base pair upstream of the transcription start site. In one embodiment, the location of a TATA box is determined using standard RNA-mapping techniques such as primer extension, S1 analysis, and/or RNase protection, to identify the position of the transcription start site within a genomic clone, and the TATA box is identified, either visually, or using a sequence search program. For example, sites important in transcriptional activation can be identified using the [publically] publicly available sequence search program TF SEARCH [(http://www.genome.ad:jp/SIT/TFSEARCH)]. Another publicly [publically] available database of sequences to which transcription factors bind is available from the National Library of Medicine in the "Transcription Data Base."

The paragraph beginning at page 37, line 5 has been amended as follows:

In order to investigate whether it was necessary to optimize the topological spacing of the HSE element relative to any of the 5 characterized important DNA/protein binding sites within the 300 base pair element of the tyrosinase promoter, plasmids were made in which the HSE element was separated from the C nucleotide at position -300 of the Tyr-300 promoter by either no nucleotides or one full turn of the DNA helix (HSE-Tyr 300-FULL) or by a stuffer fragment

representing one half turn of the helix (HSE Tyr-300-HALF) (Figure 10A [9A]). Both HSE-Tyr 300-GM-CSF plasmids transfected into MeWo melanoma cells produced the same low levels of GM-CSF as the Tyr300-GM-CSF plasmid (Figure 10B [9B]). However, when the transfected cells were heat shocked 42°C for 30 minutes, 24 hours following transfection, GM-CSF production was increased, but only in cells transfected with the HSE-Tyr300 plasmids (Figure 10B [9B]).

In the claims:

Claims 1-8, 10-14, and 16-33 have been cancelled.

Claims 9 and 15 have been amended as follows:

9. (Amended Once) A composition comprising nucleic acid, wherein said nucleic acid comprises:

(a) a cell type-specific promoter for activating the expression of a gene in a specific cell type, [The composition of claim 1,] wherein the cell type-specific promoter is human Tyr300 (SEQ ID. NO. 1);

(b) a therapeutic gene sequence operably linked to said cell type-specific promoter;

(c) an amplification promoter element for amplifying transcription of said therapeutic gene in said specific cell type; and

(d) a sequence encoding a transcription activator, said transcription activator for activating said amplification promoter element.

15. (Amended Once) A composition comprising nucleic acid, wherein said nucleic acid comprises:

(a) a cell type-specific promoter for activating the expression of a gene in a specific cell type;

(b) a therapeutic gene sequence operably linked to said cell type-specific promoter;

(c) an amplification promoter element for amplifying transcription of said therapeutic gene in said specific cell type; and

(d) a sequence encoding a transcription activator, said transcription activator for activating said amplification promoter element, [The composition of claim 1,] wherein said

nucleic acid [molecule] produces a level of mRNA expression which is at least 100-fold higher in *in vitro* cells of the specific cell type compared to *in vitro* cells which are not of the specific cell type.